

**PATENT** 3523/2/US

Ser. No. 09/933,366

Morozowich Declaration, Page 1

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Sandra M. Sims ) DOCKET NO.: 3523/2/US  
SERIAL NO.: 09/933,366 ) GROUP ART UNIT: 1614  
FILED: August 20, 2001 ) EXAMINER: Cybille Celacroix  
Muirhei

TITLE: SOLUTION COMPOSITION OF A OXAZOLIDINONE ANTIBIOTIC  
DRUG HAVING ENHANCED DRUG LOADING,

Assistant Commissioner for Patents  
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Alexandria, VA 22313-1450

**DECLARATION BY DR. WALTER MOROZOWICH, UNDER 37 CFR 1.132**

Sir:

I, Dr. Walter Morozowich, declare that:

1. I am not an inventor of the above-cited invention. However, I make this declaration in an attempt to further the prosecution of the application.
2. I received a B.S. degree in Pharmacy from Duquesne University, Pittsburgh, PA in 1955, an M.S. in Pharmaceutical Chemistry from Ohio State University, Columbus, OH in 1956, and a Ph.D. in Pharmaceutical Chemistry from Ohio State University Columbus, OH in 1959.
3. I have many years of experience in the design of salts, prodrugs and analogs, SEC formulations of poorly soluble drugs, bile acid mixed micelles, and nanoparticles. I have also focused on the prediction of physical, chemical, and biopharmaceutical properties of a variety of biologically active compounds. I began my career as a research scientist in Pharmaceutical Research at Upjohn Company in 1959. Upjohn Company eventually became Pharmacia & Upjohn Company, which later became Pharmacia Corporation, which

PATENT 3523/2/US

Ser. No. 09/933,366

Morozowich Declaration, Page 2

recently became Pfizer Inc. (hereinafter, collectively referred to as "Pfizer"). In 1984, I became a Senior Scientist V in Drug Discovery Research & Development at Pfizer. I am an author or co-author of at least 42 scientific publications and 9 review articles; I am an inventor or co-inventor on at least 43 United States patents; and I have given at least 52 external presentations at scientific meetings. I became a consultant to Pharmacia in 2000, a position I currently hold. A copy of my *curriculum vitae* is attached as Exhibit A.

4. I have reviewed a copy of the above-cited patent application, in the form of U.S. Patent Application Publication No. 20020068720 A1. I have also reviewed an Office Action from the U.S. Patent and Trademark Office, mailed March 29, 2002, and the two references cited therein, U.S. Patent Number 5,688,792 for an invention by Barbachyn *et al.* (hereinafter, "Barbachyn *et al.*") and U.S. Patent Number 5,646,294 for an invention by Bartoli *et al.* (hereinafter, "Bartoli *et al.*"). I have also read a Declaration by Michael R. Barbachyn, Under 37 CFR 1.132 (hereinafter, the "Barbachyn Declaration") submitted in prosecution of the above-cited case, dated August 29, 2002. I understand the Office Action rejected all the claims pending in the present patent application (i.e., claims 1-30) under 35 U.S.C. 103(a) as being unpatentable over Barbachyn *et al.*, 5,688,792 and in view of Bartoli *et al.*, 5,646,294." (Office Action, p. 2, item 1).
5. The Office Action specifically indicated that, at the time the present invention was made, it would have been obvious to solubilize oxazolidinone antimicrobial antibiotic drugs disclosed by Barbachyn *et al.* using a cyclodextrin disclosed by Bartoli *et al.* as being a solubilizing agent useful for solubilizing azole antifungals. I respectfully submit that the solubilization of oxazolidinones by cyclodextrins was not predictable at the time the invention was made, and in view of the two cited references, in view of evidence set forth in the Barbachyn Declaration, and in view of additional evidence presented below. The evidence presented below, furthermore, demonstrates that the solubilization of oxazolidinones by cyclodextrins is not only not predictable or expected; it is also unexpectedly high, something one would not anticipate based on lipophilicity or size considerations.

PATENT 3523/2/US

Ser. No. 09/933,366

Morozowich Declaration, Page 3

6. The Barbachyn Declaration made factual statements and presented evidence as to what was known at the time the invention was made, with regard to the physical structure of cyclodextrins, with their doughnut shape and their hydrophobic interior, and what was expected with regard to the physical characteristics and the hydrophobicities of the types of molecules that would be likely to be solubilized by such molecules. It was noted that the azole antifungal agents disclosed by Bartroli *et al.*, are considerably more hydrophobic than the oxazolidinones, such as linezolid as shown by their low log P values of about 0 to -2. As was noted in the Barbachyn Declaration, this and other differences between the two classes of compounds would lead one not to expect that the oxazolidinones, such as those disclosed by Barbachyn *et al.* to be solubilized by cyclodextrins, merely because Bartroli *et al.* states that the azole antifungal agents disclosed therein could be solubilized by at least some species of cyclodextrins. (Bartroli *et al.*, Abstract, lines 1-2, and col. 14, lines 43-48.)
7. Cyclodextrins, such as sulfobutyl- $\beta$ -cyclodextrin (SBCD) and hydroxypropyl- $\beta$ -cyclodextrin (HPCD) are known to be poor at solubilizing many drugs with low lipophilicities, (i.e., with a log P of 0 or lower) (Lofsson *et al.*, "Effects of 2-hydroxypropyl  $\beta$ -cyclodextrin on the aqueous solubility of drugs and transdermal delivery of 17 $\beta$ -estradiol," *Acta Pharm. Nord.* 1(4): 185-94 (1989); Lofsson *et al.*, "Solubilization and stabilization of drugs through cyclodextrin complexation," *Acta Pharm. Nord.* 3(4): 215-17 (1991)). Oxazolidinones are known to fall into this last class of molecules with log P values ranging from about 0 to about -2. Table 1, below, shows that the oxazolidinones have low lipophilicities with their experimentally determined log P values ranging from about 0 to -2. The oxazolidinones listed in Table 1 are the ones cited in the SciFinder abstract of U.S. Patent Application 20020068720 A1. Furthermore, the experimental log P values of the oxazolidinones claimed in Pharmacia Patent Application 20020068720 A1 are very low and, based on the literature, they should be poor substrates for complexation and solubilization by sulfobutyl- $\beta$ -cyclodextrin (SBCD) and hydroxypropyl- $\beta$ -cyclodextrin (HPCD) (Lofsson, 1991, *supra*).
8. Table 2, below, shows the solubility of various drugs, including four of the oxazolidinones from Table 1 in a 500 mg/ml solution of either SBCD or HPCD. The compound "Oxazolidinone B" in Table 2 is linezolid. Linezolid is listed on Table 2 as having a log P

**PATENT 3523/2/US**

Ser. No. 09/933,366

Morozowich Declaration, Page 4

of -0.92 and a solubility of 86 mg/ml in of HPCD (500 mg/ml) and of 59.9 mg/ml in SBCD (500 mg/ml). The solubility of linezolid in water is only 2.7 mg/ml. Note that the solubility of nitrofurantoin, with a log P value of -0.63, did not increase in the presence of HPCD as shown in the same Table. The fact that oxazolidinones are solubilized at all by cyclodextrins is surprising and unexpected, in view of the fact that the oxazolidinones have log P values of 0 to -2, and in view of the fact that nitrofurantoin, with a log P value in the same range, is not solubilized.

9. It is even more surprising and unexpected that oxazolidinones should be found to be extremely well solubilized compared to other compounds, even drug compounds with considerably higher log P values than oxazolidinones. The high degree of solubilization of oxazolidinones by cyclodextrins was illustrated in at least two examples of the present application. Example 1 of the application illustrates the solubilization of at least one oxazolidinone, linezolid, by varying amounts of SBCD. The results are shown in Table 1 of the application. Example 6 of the application illustrates the solubilization of three different oxazolidinones by varying amounts of HPCD. A plot of the results of the assay described in this last example is given in Figure 1 of the application.
10. The surprisingly high degree of solubilization of oxazolidinones by cyclodextrins is further illustrated in Table 2, below, where the solubility of four oxazolidinones is compared to that of a number of other drugs, including many drugs with considerably higher log P values than the oxazolidinones, such as retinal (log P of 6.54). Specifically, oxazolidinones A, B, C and D, from Table 1, below, were found to have solubilities ranging from 38 to 102 mg/ml in 500 mg/ml solutions of HPCD or SBCD; whereas, none of the other compounds listed in Table 2 had solubilities any higher than even the least soluble oxazolidinone listed therein.

11. Chemical structure and log P appear to be poorer predictors than expected of the degree to which other drugs can be solubilized by cyclodextrins, as well. The highest solubility of a non-oxazolidinone compound listed in Table 2, below, is that given for the steroid testosterone (38 mg/ml) in 500 mg/ml HPCD. Testosterone has a log P of 3.47. A related compound listed in Table 2, D(-)-norgesterol, has a similar log P (3.92). However, the

**PATENT 3523/2/US**

Ser. No. 09/933,366

Morozowich Declaration, Page 5

solubility of D(-)-norgesterol in the same cyclodextrin, HPCD, is surprisingly low, only 4.9 mg/ml.

12. Theoretical considerations of the factors responsible for association with the cyclodextrin cavity indicate that interaction of the hydrophobic moieties of drugs, especially phenyl moieties, with the hydrophobic interior of the cyclodextrin cavity is generally responsible for strong complexation (Connors, Kenneth A., "The Stability of Cyclodextrin Complexes in Solution", *Chem. Revs.* 97:1325-1357 (1997).). The orally active azole derivatives of Bartoli *et al.* each include at least one pendant phenyl moiety. (See, for example, the structure of Formulas I and I' in the Abstract, or in Examples 3 and 53 of Bartoli *et al.*) The oxazolidinones, however, do not have pendant aromatic groups or other similarly hydrophobic moieties; and, thus, the solubilization of oxazolidinones by cyclodextrins, particularly the high degree of such solubilization found in the formulations of the present invention, is surprising and unexpected.
13. In summary, for reasons given above, it is surprising that poorly lipophilic compounds, such as the oxazolidinone antibiotic drug in the formulations of the present invention were found to be solubilized at all by cyclodextrins, much less solubilized to the high degree illustrated in Table 2, below, and in Examples 1 and 6 of the present application.
14. For any or all of the reasons set forth herein above, therefore, I submit that it would not have been expected, neither at the time the present invention was made nor even now that one could produce a solution of an oxazolidinone antimicrobial drug, such as is disclosed by Barbachyn *et al.* and a pharmaceutically acceptable cyclodextrin compound wherein the oxazolidinone is present at a concentration above its practical limit of solubility. Specifically, it would not have been expected that cyclodextrin compounds found to be useful in solubilizing the highly lipophilic and poorly water soluble specific azole antifungal compounds, such as those described by Bartoli *et al.*, could also be used to solubilize the oxazolidinones in view of their low lipophilicities.
15. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made

**PATENT** 3523/2/US

Ser. No. 09/933,366

Morozowich Declaration, Page 6

are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of an application or any patent issuing thereon.

Walter Morozowich

Walter Morozowich

April 30, 2003

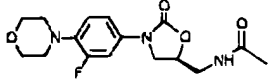
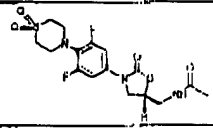
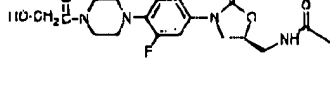
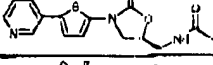
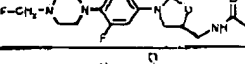
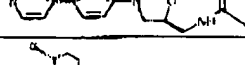
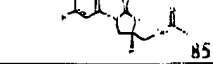
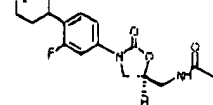
Date

**PATENT 3523/2/US**

Ser. No. 09/933,366

Morozowich Declaration, Page 7

**Table 1. Structure and Log P of the Oxazolidinones in the SciFinder Abstract of US Patent Application 20020068720 A1**

Comp. No.	Reg. No.	Structure and Name	Log P <sup>a</sup>
1	165800-03-3 (Compound 2, in Fig. 1 in US 20020068720 A1, Linezolid, PNU-100766.)	 CA Index Name: Acetamide, N-[[[(5S)-3-[3-fluoro-4-(4-morpholinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI). Other Names: Linezolid; PNU 100766; U 100766; Zyvox	-0.92
2	383199-88-0 (Compound 3, in Fig. 1 in US 20020068720 A1)	 CA Index Name: Acetamide, N-[[[(5S)-3-[4-(1,1-dioxido-4-thiomorpholinyl)-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI)	-1.61
3	Compound 1 in Figure 1 in US 20020068720 A1) Reg. Number is not in the patent	 CA Index Name: Acetamide, N-[[[(5S)-2-oxo-3-[5-(3-pyridinyl)-2-thienyl]-5-oxa-zolidinyl]methyl]- (9CI)	0.11
4	175592-48-0	 CA Index Name: Acetamide, N-[[[(5S)-3-[3-fluoro-4-[4-(2-fluoroethyl)-3-oxo-1-piperazinyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI)	0.04
5	194350-87-3	 CA Index Name: Acetamide, N-[[[(5S)-3-[4-(1,1-dioxido-4-thiomorpholinyl)-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI)	-1.46
6	225644-82-6	 CA Index Name: Acetamide, N-[[[(5S)-3-[4-(1,1-dioxido-4-thiomorpholinyl)-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI)	-2.05
7	216869-09-9, (PNU-177780)	 CA Index Name: Acetamide, N-[[[(5S)-3-[4-(1,1-dioxido-4-thiomorpholinyl)-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI)	-1.38
8	PNU-141659	 CA Index Name: Acetamide, N-[[[(5S)-3-[4-(1,1-dioxido-4-thiocyclohexyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI)	-0.62

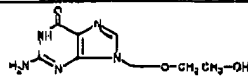
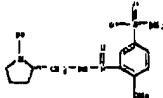
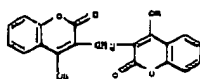
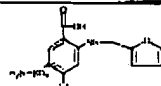
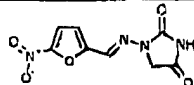
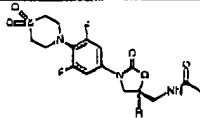
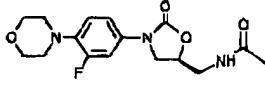
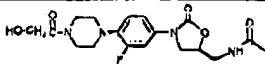
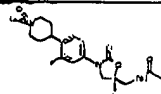
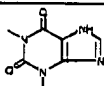
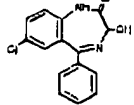
a. Log P values are taken from SciFinder for compounds 1,2,4-7. The log P values of compound 3 and compound 8 are taken from the ChemLink Database.

PATENT 3523/2/US

Ser. No. 09/933,366

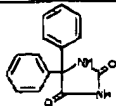
Morozowich Declaration, Page 8

**Table 2. Tabulation of the Lipophilicities and the Reported Solubilities of the Oxazolidinones and Other Drugs in Sulfobutyl- $\beta$ -Cyclodextrin (SBCD) and Hydroxypropyl- $\beta$ -Cyclodextrin (HPCD)**

Compound	Structure	SBCD or HPCD	Drug			Drug Sol. In Cyclodextrin In mg/ml		
			Sol. In Water		Lipo- philicity <sup>a</sup>	Conc. of CD (mg/ml)	Drug Sol. In CD (mg/ml)	Ref
			mg/ml	Ref.	Log P at pH 7			
Acyclovir		HPCD	1.7	d	-1.76	500	3.9	d
Sulpride		HPCD	0.21	b	-1.49	500	10.0	b
Dicoumarol		HPCD	0.15	b	-1.14	500	1.3	b
Furosemide		HPCD	0.07	b	-0.80	500	1.7	b
Nitrofurantoin		HPCD	0.2	d	-0.63	500	0.2	d
Note- No increase in solubility								
Oxazolidinone A, Reg.No.383199- 88-0, Compound 3, Table 1		HPCD	0.40	c	-1.61	500	51.6	c
Oxazolidinone B, Linezolid, PNU- 100766, Compound 2, Table 1		SBCD and HPCD	2.7	c	-0.92	500, SBCD	59.9	c
						500, HPCD	86	
Oxazolidinone C, R g.No.383199- 88-0, Compound 1, Table 1		HPCD	10	c	0.11	500	102	c
						Note - Very high solubility for the oxazolidinones		
Oxazolidinone D, PNU-141659, Compound 8, Table 1		SBCD and HPCD	0.4	g	-0.62	500, HPCD	38	g
						500, SBCD	51	
Theophylline		HPCD	8.3	b	0.04	500	11.0	b
Oxazepam.		HPCD	0.03	b	2.31	500	4.2	b



**PATENT 3523/2/US****Ser. No. 09/933,366****Morozowich Declaration, Page 9**

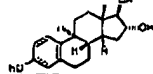
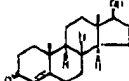
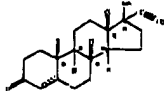
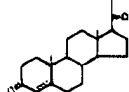
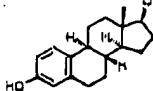

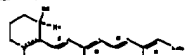
<b>Diphenylhydantoin</b>		<b>HPCD</b>	<b>0.03</b>	<b>b</b>	<b>2.49</b>	<b>500</b>	<b>9.3</b>	<b>b</b>
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**PATENT 3523/2/US**

**Ser. No. 09/933,366**

Morozowich Declaration, Page 10

**Table 2 Continued.**

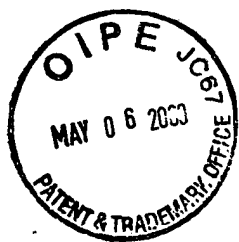
Compound	Structure	CD	H <sub>2</sub> O Sol. (mg/ml)	Ref.	Log P	CD Conc. (mg/ml)	Drug Sol in CD (mg/ml)	Ref.
Estriol		HPCD	0.003	b	2.94	500	41	b
Testosterone		HPCD	0.026	b	3.47	400	38	b
D(-)-Norgestrol		HPCD	0.002	d	3.92	500	4.9	d
Progesterone		HPCD	0.015	b	4.04	400	34	b
Estradiol		HPCD	0.004	d	4.13	500	28	d
Retinoic Acid, all Trans		HPCD	~0.07	b	4.62	400	0.8	b
Retinal		HPCD	~0.07	b	6.54	400	2.6	b

n. After May 16, vehicles will not be able to use the HOV 2 lanes in the southbound direction. <http://www.washstate.gov/transportation/traffic/traffic.html>  
 This is posted in the Southern Gateway Information Database.

1E. 11/17/70, 11/25/70, 12/10/70, 12/15/70, 12/22/70, 12/29/70, 1/5/71, 1/12/71, 1/19/71, 1/26/71, 2/2/71, 2/9/71, 2/16/71, 2/23/71, 2/30/71, 3/6/71, 3/13/71, 3/20/71, 3/27/71, 4/3/71, 4/10/71, 4/17/71, 4/24/71, 5/1/71, 5/8/71, 5/15/71, 5/22/71, 5/29/71, 6/5/71, 6/12/71, 6/19/71, 6/26/71, 7/3/71, 7/10/71, 7/17/71, 7/24/71, 7/31/71, 8/7/71, 8/14/71, 8/21/71, 8/28/71, 9/4/71, 9/11/71, 9/18/71, 9/25/71, 10/2/71, 10/9/71, 10/16/71, 10/23/71, 10/30/71, 11/6/71, 11/13/71, 11/20/71, 11/27/71, 12/4/71, 12/11/71, 12/18/71, 12/25/71, 1/1/72, 1/8/72, 1/15/72, 1/22/72, 1/29/72, 2/5/72, 2/12/72, 2/19/72, 2/26/72, 3/5/72, 3/12/72, 3/19/72, 3/26/72, 4/2/72, 4/9/72, 4/16/72, 4/23/72, 4/30/72, 5/7/72, 5/14/72, 5/21/72, 5/28/72, 6/4/72, 6/11/72, 6/18/72, 6/25/72, 7/2/72, 7/9/72, 7/16/72, 7/23/72, 7/30/72, 8/6/72, 8/13/72, 8/20/72, 8/27/72, 9/3/72, 9/10/72, 9/17/72, 9/24/72, 10/1/72, 10/8/72, 10/15/72, 10/22/72, 10/29/72, 11/5/72, 11/12/72, 11/19/72, 11/26/72, 12/3/72, 12/10/72, 12/17/72, 12/24/72, 1/1/73, 1/8/73, 1/15/73, 1/22/73, 1/29/73, 2/5/73, 2/12/73, 2/19/73, 2/26/73, 3/5/73, 3/12/73, 3/19/73, 3/26/73, 4/2/73, 4/9/73, 4/16/73, 4/23/73, 4/30/73, 5/7/73, 5/14/73, 5/21/73, 5/28/73, 6/4/73, 6/11/73, 6/18/73, 6/25/73, 7/2/73, 7/9/73, 7/16/73, 7/23/73, 7/30/73, 8/6/73, 8/13/73, 8/20/73, 8/27/73, 9/3/73, 9/10/73, 9/17/73, 9/24/73, 10/1/73, 10/8/73, 10/15/73, 10/22/73, 10/29/73, 11/5/73, 11/12/73, 11/19/73, 11/26/73, 12/3/73, 12/10/73, 12/17/73, 12/24/73, 1/1/74, 1/8/74, 1/15/74, 1/22/74, 1/29/74, 2/5/74, 2/12/74, 2/19/74, 2/26/74, 3/5/74, 3/12/74, 3/19/74, 3/26/74, 4/2/74, 4/9/74, 4/16/74, 4/23/74, 4/30/74, 5/7/74, 5/14/74, 5/21/74, 5/28/74, 6/4/74, 6/11/74, 6/18/74, 6/25/74, 7/2/74, 7/9/74, 7/16/74, 7/23/74, 7/30/74, 8/6/74, 8/13/74, 8/20/74, 8/27/74, 9/3/74, 9/10/74, 9/17/74, 9/24/74, 10/1/74, 10/8/74, 10/15/74, 10/22/74, 10/29/74, 11/5/74, 11/12/74, 11/19/74, 11/26/74, 12/3/74, 12/10/74, 12/17/74, 12/24/74, 1/1/75, 1/8/75, 1/15/75, 1/22/75, 1/29/75, 2/5/75, 2/12/75, 2/19/75, 2/26/75, 3/5/75, 3/12/75, 3/19/75, 3/26/75, 4/2/75, 4/9/75, 4/16/75, 4/23/75, 4/30/75, 5/7/75, 5/14/75, 5/21/75, 5/28/75, 6/4/75, 6/11/75, 6/18/75, 6/25/75, 7/2/75, 7/9/75, 7/16/75, 7/23/75, 7/30/75, 8/6/75, 8/13/75, 8/20/75, 8/27/75, 9/3/75, 9/10/75, 9/17/75, 9/24/75, 10/1/75, 10/8/75, 10/15/75, 10/22/75, 10/29/75, 11/5/75, 11/12/75, 11/19/75, 11/26/75, 12/3/75, 12/10/75, 12/17/75, 12/24/75, 1/1/76, 1/8/76, 1/15/76, 1/22/76, 1/29/76, 2/5/76, 2/12/76, 2/19/76, 2/26/76, 3/5/76, 3/12/76, 3/19/76, 3/26/76, 4/2/76, 4/9/76, 4/16/76, 4/23/76, 4/30/76, 5/7/76, 5/14/76, 5/21/76, 5/28/76, 6/4/76, 6/11/76, 6/18/76, 6/25/76, 7/2/76, 7/9/76, 7/16/76, 7/23/76, 7/30/76, 8/6/76, 8/13/76, 8/20/76, 8/27/76, 9/3/76, 9/10/76, 9/17/76, 9/24/76, 10/1/76, 10/8/76, 10/15/76, 10/22/76, 10/29/76, 11/5/76, 11/12/76, 11/19/76, 11/26/76, 12/3/76, 12/10/76, 12/17/76, 12/24/76, 1/1/77, 1/8/77, 1/15/77, 1/22/77, 1/29/77, 2/5/77, 2/12/77, 2/19/77, 2/26/77, 3/5/77, 3/12/77, 3/19/77, 3/26/77, 4/2/77, 4/9/77, 4/16/77, 4/23/77, 4/30/77, 5/7/77, 5/14/77, 5/21/77, 5/28/77, 6/4/77, 6/11/77, 6/18/77, 6/25/77, 7/2/77, 7/9/77, 7/16/77, 7/23/77, 7/30/77, 8/6/77, 8/13/77, 8/20/77, 8/27/77, 9/3/77, 9/10/77, 9/17/77, 9/24/77, 10/1/77, 10/8/77, 10/15/77, 10/22/77, 10/29/77, 11/5/77, 11/12/77, 11/19/77, 11/26/77, 12/3/77, 12/10/77, 12/17/77, 12/24/77, 1/1/78, 1/8/78, 1/15/78, 1/22/78, 1/29/78, 2/5/78, 2/12/78, 2/19/78, 2/26/78, 3/5/78, 3/12/78, 3/19/78, 3/26/78, 4/2/78, 4/9/78, 4/16/78, 4/23/78, 4/30/78, 5/7/78, 5/14/78, 5/21/78, 5/28/78, 6/4/78, 6/11/78, 6/18/78, 6/25/78, 7/2/78, 7/9/78, 7/16/78, 7/23/78, 7/30/78, 8/6/78, 8/13/78, 8/20/78, 8/27/78, 9/3/78, 9/10/78, 9/17/78, 9/24/78, 10/1/78, 10/8/78, 10/15/78, 10/22/78, 10/29/78, 11/5/78, 11/12/78, 11/19/78, 11/26/78, 12/3/78, 12/10/78, 12/17/78, 12/24/78, 1/1/79, 1/8/79, 1/15/79, 1/22/79, 1/29/79, 2/5/79, 2/12/79, 2/19/79, 2/26/79, 3/5/79, 3/12/79, 3/19/79, 3/26/79, 4/2/79, 4/9/79, 4/16/79, 4/23/79, 4/30/79, 5/7/79, 5/14/79, 5/21/79, 5/28/79, 6/4/79, 6/11/79, 6/18/79, 6/25/79, 7/2/79, 7/9/79, 7/16/79, 7/23/79, 7/30/79, 8/6/79, 8/13/79, 8/20/79, 8/27/79, 9/3/7

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2. H. Hoffmann, in: *Handb. Math. Physik*, Bd. 1, 1958, S. 123-124, 125-126, 127-128, 129-130, 131-132, 133-134, 135-136, 137-138, 139-140, 141-142, 143-144, 145-146, 147-148, 149-150, 151-152, 153-154, 155-156, 157-158, 159-160, 161-162, 163-164, 165-166, 167-168, 169-170, 171-172, 173-174, 175-176, 177-178, 179-180, 181-182, 183-184, 185-186, 187-188, 189-190, 191-192, 193-194, 195-196, 197-198, 199-200, 201-202, 203-204, 205-206, 207-208, 209-210, 211-212, 213-214, 215-216, 217-218, 219-220, 221-222, 223-224, 225-226, 227-228, 229-230, 231-232, 233-234, 235-236, 237-238, 239-240, 241-242, 243-244, 245-246, 247-248, 249-250, 251-252, 253-254, 255-256, 257-258, 259-260, 261-262, 263-264, 265-266, 267-268, 269-270, 271-272, 273-274, 275-276, 277-278, 279-280, 281-282, 283-284, 285-286, 287-288, 289-290, 291-292, 293-294, 295-296, 297-298, 299-300, 301-302, 303-304, 305-306, 307-308, 309-310, 311-312, 313-314, 315-316, 317-318, 319-320, 321-322, 323-324, 325-326, 327-328, 329-330, 331-332, 333-334, 335-336, 337-338, 339-340, 341-342, 343-344, 345-346, 347-348, 349-350, 351-352, 353-354, 355-356, 357-358, 359-360, 361-362, 363-364, 365-366, 367-368, 369-370, 371-372, 373-374, 375-376, 377-378, 379-380, 381-382, 383-384, 385-386, 387-388, 389-390, 391-392, 393-394, 395-396, 397-398, 399-400, 401-402, 403-404, 405-406, 407-408, 409-410, 411-412, 413-414, 415-416, 417-418, 419-420, 421-422, 423-424, 425-426, 427-428, 429-430, 431-432, 433-434, 435-436, 437-438, 439-440, 441-442, 443-444, 445-446, 447-448, 449-450, 451-452, 453-454, 455-456, 457-458, 459-460, 461-462, 463-464, 465-466, 467-468, 469-470, 471-472, 473-474, 475-476, 477-478, 479-480, 481-482, 483-484, 485-486, 487-488, 489-490, 491-492, 493-494, 495-496, 497-498, 499-500, 501-502, 503-504, 505-506, 507-508, 509-510, 511-512, 513-514, 515-516, 517-518, 519-520, 521-522, 523-524, 525-526, 527-528, 529-530, 531-532, 533-534, 535-536, 537-538, 539-540, 541-542, 543-544, 545-546, 547-548, 549-550, 551-552, 553-554, 555-556, 557-558, 559-560, 561-562, 563-564, 565-566, 567-568, 569-570, 571-572, 573-574, 575-576, 577-578, 579-580, 581-582, 583-584, 585-586, 587-588, 589-590, 591-592, 593-594, 595-596, 597-598, 599-600, 601-602, 603-604, 605-606, 607-608, 609-610, 611-612, 613-614, 615-616, 617-618, 619-620, 621-622, 623-624, 625-626, 627-628, 629-630, 631-632, 633-634, 635-636, 637-638, 639-640, 641-642, 643-644, 645-646, 647-648, 649-650, 651-652, 653-654, 655-656, 657-658, 659-660, 661-662, 663-664, 665-666, 667-668, 669-670, 671-672, 673-674, 675-676, 677-678, 679-680, 681-682, 683-684, 685-686, 687-688, 689-690, 691-692, 693-694, 695-696, 697-698, 699-700, 701-702, 703-704, 705-706, 707-708, 709-710, 711-712, 713-714, 715-716, 717-718, 719-720, 721-722, 723-724, 725-726, 727-728, 729-730, 731-732, 733-734, 735-736, 737-738, 739-740, 741-742, 743-744, 745-746, 747-748, 749-750, 751-752, 753-754, 755-756, 757-758, 759-760, 761-762, 763-764, 765-766, 767-768, 769-770, 771-772, 773-774, 775-776, 777-778, 779-780, 781-782, 783-784, 785-786, 787-788, 789-790, 791-792, 793-794, 795-796, 797-798, 799-800, 801-802, 803-804, 805-806, 807-808, 809-810, 811-812, 813-814, 815-816, 817-818, 819-820, 821-822, 823-824, 825-826, 827-828, 829-830, 831-832, 833-834, 835-836, 837-838, 839-840, 841-842, 843-844, 845-846, 847-848, 849-850, 851-852, 853-854, 855-856, 857-858, 859-860, 861-862, 863-864, 865-866, 867-868, 869-870, 871-872, 873-874, 875-876, 877-878, 879-880, 881-882, 883-884, 885-886, 887-888, 889-890, 891-892, 893-894, 895-896, 897-898, 899-900, 901-902, 903-904, 905-906, 907-908, 909-910, 911-912, 913-914, 915-916, 917-918, 919-920, 921-922, 923-924, 925-926, 927-928, 929-930, 931-932, 933-934, 935-936, 937-938, 939-940, 941-942, 943-944, 945-946, 947-948, 949-950, 951-952, 953-954, 955-956, 957-958, 959-960, 961-962, 963-964, 965-966, 967-968, 969-970, 971-972, 973-974, 975-976, 977-978, 979-980, 981-982, 983-984, 985-986, 987-988, 989-990, 991-992, 993-994, 995-996, 997-998, 999-1000, 1001-1002, 1003-1004, 1005-1006, 1007-1008, 1009-1010, 1011-1012, 1013-1014, 1015-1016, 1017-1018, 1019-102

**RECEIVED**

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TECH CENTER 1600/2900

**PATENT** 3523/2/US

Ser. No. 09/933,366

Exhibit A, Page 1

**CURRICULUM VITAE FOR WALTER MOROZOWICH, Ph. D.****EDUCATION**

- 1959            Ph.D., Pharmaceutical Chemistry, Ohio State University, Columbus, OH;  
Thesis: Synthesis and Chelation of Sulfonylureas Related to Tolbutamide  
(Professor F.W. Bope, advisor)
- 1956            M.S., Pharmaceutical Chemistry, Ohio State University, Columbus, OH;  
Thesis: Synthesis of 8-Nitrotheophylline Salts (Professor F.W. Bope,  
advisor)
- 1955            B.S., Pharmacy, Duquesne University, Pittsburg, PA

**EMPLOYMENT HISTORY**

- 2000-present    Pharmacia Corporation  
Consultant
- 1998-2000       Pharmacia & Upjohn  
Senior Scientist V in Pharm. Development, Experimental Formulations
- 1996-1998       Pharmacia & Upjohn  
Senior Scientist V in Pharm. Development, Solid Forms
- 1993-1995       Pharmacia & Upjohn and The Upjohn Company  
Senior Scientist V in Drug Discovery Research & Development,  
Specialty Products
- 1989-1993       The Upjohn Company  
Senior Scientist V in Drug Discovery Research & Development,  
Pharmaceutics
- 1984-1989       The Upjohn Company  
Senior Scientist V in Drug Discovery Research & Development,  
Drug Delivery Systems
- 1959-1984       The Upjohn Company  
Pharmaceutical Research

**PATENT 3523/2/US**

Ser. No. 09/933,366

Exhibit A, Page 2

**HONORS**

Outstanding Achievement Award, Duquesne University - 1995  
Upjohn Achievement in Science and Medicine Award - 1990  
W. E. Upjohn Award - 1971

**PROFESSIONAL MEMBERSHIPS**

Academy of Pharmaceutical Sciences  
American Chemical Society

**CURRENT AREAS OF SCIENTIFIC INTEREST**

Prediction of physical-chemical/biopharmaceutical properties; design of salts, prodrugs and analogs; SEC formulations of poorly soluble drugs; bile acid mixed micelles; and nanoparticles.

**PATENTS**

Inventor or co-inventor of at least 43 U.S. patents

**PUBLICATIONS**

Author or co-author of at least 42 scientific publications  
Author or co-author of at least 9 review articles

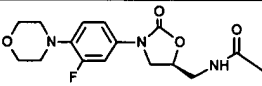
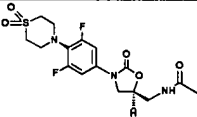
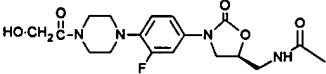
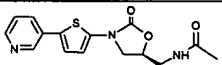
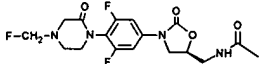
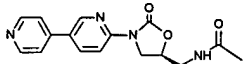
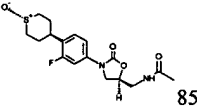
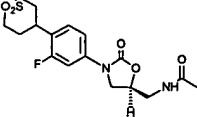
**INVITED PRESENTATIONS, BOOKS, SYMPOSIA**

Gave at least 12 invited oral scientific presentations  
Co-edited one book and assisted in the writing of a second book.  
Organized at least one scientific symposium

**EXTERNAL ORAL & POSTER PRESENTATIONS**

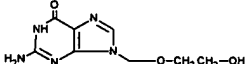
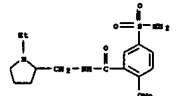
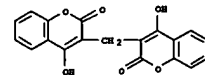
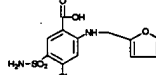
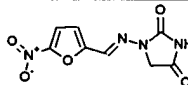
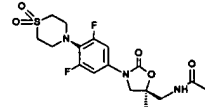
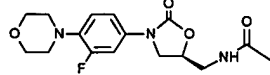
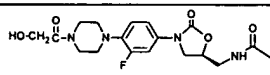
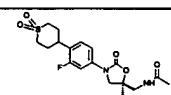
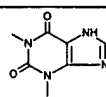
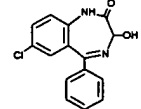
Gave at least 52 external oral and/or poster presentations at scientific meetings.

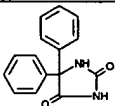
**Table 1. Structure and Log P of the Oxazolidinones in the SciFinder Abstract of US Patent Application 20020068720 A1**

Comp. No.	Reg. No.	Structure and Name		Log P <sup>a</sup>
1	<b>165800-03-3</b> (Compound 2, in Fig. 1 in US 20020068720 A1, <b>Linezolid</b> , PNU-100766,)		CA Index Name: Acetamide, N-[(5S)-3-[3-fluoro-4-(4-morpholinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI). Other Names: Linezolid; PNU 100766; U 100766; Zyvox	-0.92
2	<b>383199-88-0</b> (Compound 3, in Fig. 1 in US 20020068720 A1)		CA Index Name: Acetamide, N-[(5S)-3-[4-(1,1-dioxido-4-thiomorpholinyl)-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI)	-1.61
3	Compound 1 in Figure 1 in US 20020068720 A1) Reg. Number is not in the patent		CA Index Name: Acetamide, N-[(rS)-3-[fluoro-4-(4-(hydroxyacetyl)-1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]- (9 CI)	0.11
4	<b>175592-48-0</b>		CA Index Name: Acetamide, N-[(5S)-2-oxo-3-[5-(3-pyridinyl)-2-thienyl]-5-oxa-zolidinyl]methyl]- (9CI)	0.04
5	<b>194350-87-3</b>		CA Index Name: Acetamide, N-[(5S)-3-[3-fluoro-4-[4-(2-fluoroethyl)-3-oxo-1-piperazinyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI)	-1.46
6	<b>225644-82-6</b>		CA Index Name: Acetamide, N-[(5S)-3-[3-[3,4'-bipyridin]-6-yl]-2-oxo-5-oxazolidinyl] methyl]-, monohydrochloride (9CI)	-2.05
7	<b>216869-09-9</b> , (PNU-177780)		Not in the Patent. CA Index Name: Acetamide, N-[(5S)-3-[4-(1-oxido-4-thiomorpholinyl)-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI)	-1.38
8	<b>PNU-141659</b>		Not in the Patent. CA Index Name: Acetamide, N-[(5S)-3-[4-(1,1-dioxido-4-thiocyclohexyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI)	-0.62

a. Log P values are taken from SciFinder for compounds 1,2,4-7. The log P values of compound 3 and compound 8 are taken from the ChemLink Database.

**Table 2. Tabulation of the Lipophilicities and the Reported Solubilities of the Oxazolidinones and Other Drugs in Sulfobutyl- $\beta$ -Cyclodextrin (SBCD) and Hydroxypropyl- $\beta$ -Cyclodextrin (HPCD)**

Compound	Structure	SBCD or HPCD	Drug			Drug Sol. In Cyclodextrin in mg/ml		
			Sol. In Water		Lipo- philicity <sup>a</sup>	Conc. of CD (mg/ml)	Drug Sol. In CD (mg/ml)	Ref
			mg/ml	Ref.	Log P at pH 7			
Acyclovir		HPCD	1.7	d	-1.76	500	3.9	d
Sulpride		HPCD	0.21	b	-1.49	500	10.0	b
Dicoumarol		HPCD	0.15	b	-1.14	500	1.3	b
Furosemide		HPCD	0.07	b	-0.80	500	1.7	b
Nitrofurantoin		HPCD	0.2	d	-0.63	500	0.2	d
Note- No increase in solubility								
Oxazolidinone A, Reg.No.383199- 88-0, Compound 3, Table 1		HPCD	0.40	c	-1.61	500	51.6	c
Oxazolidinone B, Linezolid, PNU- 100766, Compound 2, Table 1		SBCD and HPCD	2.7	c	-0.92	500, SBCD	59.9	c
						500, HPCD	86	
Oxazolidinone C, Reg.No.383199- 88-0, Compound 1, Table 1		HPCD	10	c	0.11	500	102	c
						Note – Very high solubility for the oxazolidinones		
Oxazolidinone D, PNU-141659, Compound 8, Table 1		SBCD and HPCD	0.4	g	- 0.62	500, HPCD	38	g
						500, SBCD	51	
Theophylline		HPCD	8.3	b	0.04	500	11.0	b
Oxazepam.		HPCD	0.03	b	2.31	500	4.2	b

Diphenylhydantoin		HPCD	0.03	b	2.49	500	9.3	b
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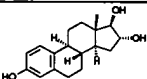
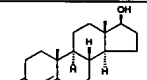
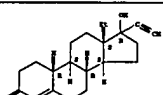
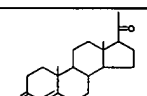
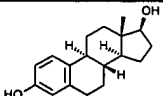
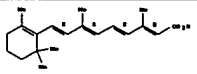
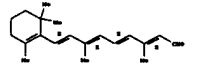
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Morozowich Declaration, Page 10

TECH CENTER 1600/2900

Table 2 Continued.

Compound	Structure	CD	H <sub>2</sub> O Sol. (mg/ml)	Ref.	Log P	CD Conc. (mg/ml)	Drug Sol in CD (mg/ml)	Ref.
Estriol		HPCD	0.003	b	2.94	500	41	b
Testosterone		HPCD	0.026	b	3.47	400	38	b
D(-)-Norgestrol		HPCD	0.002	d	3.92	500	4.9	d
Progesterone		HPCD	0.015	b	4.04	400	34	b
Estradiol		HPCD	0.004	d	4.13	500	28	d
Retinoic Acid, all Trans		HPCD	~0.07	b	4.62	400	0.8	b
Retinal		HPCD	~0.07	b	6.54	400	2.6	b

a. The log P values at pH 7 are taken from the ACD/pKa Database, [http://www.acdlabs.com/products/phys\\_chem\\_lab/pka/exp.html](http://www.acdlabs.com/products/phys_chem_lab/pka/exp.html). This is provided in the SciFinder (ACS) literature database.

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